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EXAMINER	
LEFFERS JR, GERALD G	

ART UNIT	PAPER NUMBER
1636	14

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/800,520	IBA ET AL.	
	Examiner	Art Unit	
	Gerald G Leffers Jr.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 November 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *34-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. *09/214,465* .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *13* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Receipt is acknowledged of an amendment, filed 11/25/02 as Paper No. 12, in which claims were cancelled (claims 8 & 9) and in which new claims were added (claims 34-39).

Claims 34-39 are pending and under consideration in the instant action.

Response to Amendment

The response filed in Paper No. 12 has significantly broadened the scope of the claimed invention by deleting any explicit linkage of the mRNA-destabilizing sequence with the drug-resistance gene that is used as a selectable marker. This raises new issues under 35 U.S.C. 112, 1st and 2nd paragraphs, as well as making the claims read on additional prior art. Any rejection of record in the previous office action (Paper No. 11 mailed 8/23/02) not addressed in the instant action is withdrawn. This action is FINAL.

Oath/Declaration

Receipt is acknowledged of a copy of a declaration originally filed in the parent application of which the instant application is a Continuation Application. This response is sufficient to overcome the objection to the Declaration made in the previous office action.

Information Disclosure Statement

The information disclosure statement filed 11/25/02 as Paper No. 13 has been fully considered. The signed and initialed PTO Form 1449 has been mailed with this action.

Claim Objections

Claims 34-36 are objected to because of the following informalities: the phrase "a mRNA-destabilizing sequence" is grammatically incorrect. It would be remedial to substitute "an" for the word "a" in the cited phrase. Appropriate correction is required.

Claim 36 is objected to because of the following informalities: there is no article (i.e. "a") between the words "of" and "non-translated". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 34-39 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new rejection, necessitated by applicants' amendment of the claims in Paper No. 12.**

Claims 34-39 are directed to an expression vector comprising a drug resistance gene as a selection marker and an mRNA-destabilizing sequence. There is no explicit linkage between the mRNA-destabilizing sequence and the gene encoding the drug resistance gene that is used as a selection marker. Thus, as currently written, the claims encompass a very broad range of vectors that comprise a drug resistance gene that can be used as a selectable marker and a drug resistance

gene. The originally filed specification and claims are directed to a much more narrow range of vectors where the mRNA-destabilizing sequence and drug-resistance gene are physically linked so that the resulting hybrid mRNA encoding a selectable marker has a shortened half-life in a host cell (e.g. page 22 of the instant specification, 1st full paragraph; cancelled claims 8-9). Therefore, the broader range encompassed by the newly submitted claims is impermissible NEW MATTER.

Claim 39 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 39 is directed towards a method of producing cells that highly express gene products encoded by an expression vector comprising the step of transferring the expression vector into the cells. The claim is extremely broad in scope in that it contemplates the use of the hybrid drug resistance gene comprising an mRNA-destabilizing sequence in transformation and selection of any cell type with any vector. However, in the specification, the short-lived transcript drug resistance genes are only described in the context of selecting cells comprising very specific expression constructs integrated into the host cell genome fro the purpose of preparing pre-packaging cells useful for the preparation of retroviral gene transfer vectors (e.g. pages 16-17, bridging paragraph; page 22, 1st paragraph). No broader use for the recited short-lived transcript drug resistance genes is contemplated in the originally filed specification or

claims. Thus, the broader scope of use encompassed by the newly added claim is impermissible NEW MATTER.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 34-39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **These are new rejections, necessitated by applicants' amendment of the claims in Paper No. 12.**

Claim 35 is vague and indefinite in that the metes and bounds of the term "highly express" is unclear. This is a subjective term that is not clearly defined in the instant specification. How much of the desired gene product has to be expressed in a given cell for the vector to be considered as "highly" expressing the desired gene product? It would be remedial to amend the claim to clearly indicate exactly what are the metes and bounds of "highly expressing" the desired gene product.

Claim 39 is vague and indefinite in that the metes and bounds of the term "highly expressing" are unclear. This is a subjective term that is not clearly defined in the instant specification. How much of the desired gene product has to be expressed in a given cell for the vector to be considered as "highly" expressing the desired gene product? It would be remedial to amend the claim to clearly indicate exactly what are the metes and bounds of "highly expressing" the desired gene product.

New claims 34-39 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01.

The omitted structural cooperative relationships are: any explicit linkage between the mRNA-destabilizing sequence and the drug resistance gene. Applicants' specification makes clear that the critical element of the short-lived transcript drug resistance genes of the invention is the operative linkage of an mRNA-destabilizing sequence to the coding sequence for the drug resistance gene such that the resulting hybrid mRNA has a reduced half-life in the cell (e.g. the newly submitted Abstract; page 22 of the instant specification, 1st full paragraph; original claims 8 & 9). It would be remedial to amend the claim language to explicitly indicate the operative linkage of the mRNA-destabilizing sequence to the coding sequence for the drug resistance gene.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The rejected claims are drawn towards expression vectors comprising a drug resistance gene as a selection marker and an mRNA destabilizing sequence (e.g. claim 34). The vector can be one intended to "highly express" gene products encoded by the vector through transfection of host cells with the vector and selection of cells comprising the vector with the drug (e.g. claim 35). The mRNA destabilizing sequence can be obtained from the untranslated region of a gene encoding c-fos (e.g. claim 36). Cells comprising the expression vector are claimed (claim 38) as well as a method of producing cells for "highly expressing" gene products encoded by the expression vector comprising transforming the host cells with the vector (claim 39).

The intended use language of claim 35 does not convey a defined structural, functional characteristic to the claimed vector and adds no patentable weight to the claim (i.e. "wherein said expression vector is a vector for producing cells which highly express gene products encoded by said vector, through transfecting cells with said vector and selecting cells with said drug"). Also, the term "highly express" as applied to protein expression is not clearly defined in the specification, is inherently indefinite (see above), and does not add any meaningful limitation to the claim. The absence of any explicit linkage in claims 34-35 between the mRNA destabilizing sequence and the gene encoding the drug resistance factor results in the claims reading on any expression vector comprising 1) a drug resistance gene that may be used as a selection marker (e.g. amp^r or tet^r) and 2) an mRNA-destabilizing sequence.

The first of the following rejections is directed explicitly towards those embodiments wherein the mRNA-destabilizing sequence and drug resistance gene are not operatively linked.

The grounds of the final three rejections are based upon the embodiments of the claimed invention, still encompassed by the rejected claims, wherein the mRNA-destabilizing sequence is in fact operatively linked to the gene encoding the drug resistance factor. A rejection directed towards embodiments wherein the two coding sequences are operatively linked was made in the previous office action and is still applicable, particularly since the operative linkage of the mRNA-destabilizing sequence to the drug resistance gene is the critical structural/functional element of the claimed invention (see above under 112 2nd paragraph rejections). A response to applicants' arguments over this type of rejection made in the previous office action and based upon the teachings of the Pavlakis et al patent follows.

Claims 34-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pavlakis et al (U.S. Patent No. 5,972,596; see the entire patent) in view of the 1995 Pharmacia Biotech catalog (Pharmacia Biotech Inc., see all of pages 128-129). **This is a new rejection. This rejection is directed towards embodiments wherein the drug resistance gene is not operatively linked to the mRNA-destabilizing sequence, but is present on the vector as a selectable marker.**

The Pavlakis patent (the '596 patent) teaches methods for identifying and correcting inhibitory/instability sequences (INS) within the coding region of an mRNA of a desired protein such that the level of production of the desired protein can be increased (e.g. Abstract; columns 5-6, bridging paragraph). Pavlakis et al teach that in order to evaluate whether putative regulatory sequences are sufficient to confer mRNA stability control (e.g. destabilization) on an mRNA transcript, DNA sequences coding for the suspected INS region are fused to an indicator

(or reporter) gene to create a gene coding for a hybrid mRNA. The DNA sequence fused to the indicator gene can be cDNA, genomic DNA or synthesized DNA. Examples of acceptable reporter genes known in the art are genes encoding neomycin resistance protein (note: neomycin itself is not a protein), B-galactosidase, chloramphenicol resistance, luciferase, B-globin, PGK1 and ACT1.

The '596 patent teaches that the stability and/or utilization of the mRNAs generated by fusion of the indicator genes and sequences suspected of encoding an INS region is tested by transfecting the hybrid genes into host cells which are appropriate for the expression vector used to clone and express the mRNAs. The resulting levels of mRNA are determined by standard methods of determining mRNA stability (e.g. Northern blots, S1 nuclease mapping or PCR methods), and the resulting levels of protein produced are quantitated by protein measuring assays (e.g. ELISA, western blot, etc.). The INS regions are identified by a decrease in the protein expression and/or stability of the hybrid mRNA as compared to the control indicator RNA (e.g. column 13, lines 44-62). Once INS regions of a particular target gene are identified, the coding sequence can be altered such that the expressed polypeptide is the same one encoded by the original coding sequence, or a conservative variant of the original polypeptide (e.g. column 16, section 3). Mutated or altered coding sequences designed to remove INS sequences are then tested in the same manner as was used to identify the INS sequence (e.g. column 16, lines 45-56).

The Pavlakis et al patent teaches that genes encoding or suspected of encoding mRNAs containing inhibitory/instability regions within the coding region are particularly relevant to the invention (column 12, lines 34-36). In particular, c-fos is identified as a protein whose coding

sequence is known in the art to comprise INS sequences that result in the c-fos transcript being unstable such that it is rapidly degraded (e.g. column 2, lines 8-13; column 12, lines 15-35). Example 3 is directed towards an embodiment wherein fragments encoding c-fos are operatively linked to a sequence encoding a reporter protein (i.e. RSV gag).

Pavlakis et al do not explicitly teach that any of their expression constructs use neomycin resistance or chloramphenicol resistance genes as selectable markers.

The 1995 Pharmacia Biotech catalog teaches that genes encoding drug resistance factors were known in the art at the time of filing and are useful for the selection of transformed prokaryotic cells (e.g. amp^r, kan^r and $chloramphenicol^r$ genes) and/or eukaryotic cells (e.g. the neo^r gene on pNEO) (pages 128-129). For example, the catalog teaches that the neo^r gene on pNEO can be excised and put into another recombinant vector and used as a dominant selectable marker to select transformed cells in a variety of different plant and mammalian cell types (pNEO, lines 5-8).

It would have been obvious to modify the vectors taught by Pavlakis et al for identification of INS sequences to include an appropriate bacterial or eukaryotic selectable marker in order to allow the selection of transformed cells for the purpose of plasmid amplification and/or use in the screening methods taught by Pavlakis et al. One would have been motivated to do so in order to receive the expected benefit of being able to select from a mixed population of cells those cells transformed with the desired expression construct to be used in the INS screening methods taught by Pavlakis et al. Absent any evidence to the contrary, there would have been a reasonable expectation of success in incorporating one of the selectable

marker genes taught by the Pharmacia catalog into one of the vectors taught by Pavlakis et al in order to allow the selection of transformed cells in either bacterial or eukaryotic cell types.

Claims 34-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pavlakis et al (U.S. Patent No. 5,972,596; see the entire patent) in view of DePonti-Zilli et al (PNAS USA 1988, Vol. 85, pages 1389-1393; see the entire reference). **This a new rejection necessitated by applicants' amendment of the claims in Paper No. 12. The grounds for this rejection are similar to those given for rejecting original claims 8-9 in Paper No. 11, mailed 8/23/02. The grounds of this rejection are directed to the embodiments embraced by the rejected claims, and previously specifically recited, wherein the mRNA-destabilizing sequence is operatively linked to the drug resistance gene.**

The teachings of the Pavlakis et al patent are described above and applied as before, except: the Pavlakis et al patent does not exemplify an embodiment where the neomycin resistance gene is operatively linked to a coding sequence comprising an INS, although it does suggest that the neomycin resistance gene would be an effective reporter in their system. The '596 patent doesn't explicitly teach the fusion of a coding sequence for neomycin resistance to any part of the c-fos gene.

The DePonti-Zilli et al reference teaches the characterization of a 40 base-pair sequence in the 3' end of the B-actin gene with regard to regulating B-actin mRNA transcription during myogenesis (e.g. Abstract). DePonti-Zilli et al teach that fusion of the 40 base-pair sequence 3' to the genes for a-cardiac-actin and neomycin-resistance protein confers the B-actin mRNA regulatory pattern on the hybrid constructs when introduced into C2C12 cells (e.g. Abstract;

Figure 3). Hybrid transcript levels were detected by S1 nuclease protection assays using end-labeled neomycin resistance gene probes (e.g. page 1389, column 2, "RNA Isolation and Nuclease S1 Analysis"; Figure 3). The authors conclude that although the 40 base-pair sequence from B-actin fused to the neomycin resistance coding sequence conferred B-actin transcriptional regulatory patterns on the hybrid transcript, the control was not at the level of RNA stability (e.g. pages 1392-1393, bridging paragraph). Therefore, DePonti-Zilli et al do not teach the construction and use of a short-lived transcript drug resistance gene.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the neomycin resistance gene in the methods of Pavlakis et al as an indicator to identify instability sequences (INS) of a gene encoding a transcript known or suspected to possess such INS sequences because Pavlakis et al teach it is within the skill of the art to use the gene encoding neomycin resistance as a reporter gene to identify such instability sequences and because DePonti-Zilli et al teach the use of the neomycin resistance gene to characterize a putative transcriptional regulatory sequence when the putative regulatory sequence is fused to the sequence encoding neomycin resistance. One would have been motivated to do so in order to receive the expected benefit, as suggested by Pavlakis et al and actually exemplified by DePonti-Zilli et al, of being able to characterize the ability of a putative transcriptional regulatory sequence to affect the stability/utilization of a neomycin resistance gene transcript. Absent any evidence to the contrary, there would have been a reasonable expectation of success in utilizing the neomycin resistance gene as a marker to identify transcriptional regulatory sequences that destabilize the neomycin resistance transcript. In cases in which such a destabilizing element is

identified using the neomycin resistance gene as a reporter, one would necessarily have generated a short-lived transcript drug resistance gene.

The limitation of "a drug resistance gene, as a selection marker", while not indefinite, is extremely broad, encompassing any arrangement and selection conditions wherein the drug resistance gene can be used in a given cell type to select for cells comprising the vector. Structurally, the limitation implies that the resistance factor expressed by the resistance gene is functional, and that the coding sequence for the drug resistance factor is operatively linked to a promoter active in at least one cell type. There is no further limitation regarding under what conditions the drug resistance gene is usable as a selectable marker (e.g. cell type, drug levels). Vectors made according to the teachings of the references cited above would include embodiments wherein the INS sequence attached to the neomycin coding sequence would not result in inactivation of the neomycin resistance factor (e.g. attachment of the c-fos 3' untranslated INS element to the neo^r gene). Such embodiments would be structurally/functionally indistinguishable from the claimed vector.

Claims 34-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pavlakis et al (U.S. Patent No. 5,972,596; see the entire patent) in view of Gritz et al (Gene 1983, Vol. 25, pages179-188). **This is a new rejection. The grounds of this rejection are directed to the embodiments embraced by the rejected claims, and previously specifically recited, wherein the mRNA-destabilizing sequence is operatively linked to the hygromycin resistance gene.**

The teachings of the Pavlakis et al patent (the '596 patent) are described above and applied as before, except: the Pavlakis et al patent does not explicitly teach an embodiment

where the hygromycin resistance gene is operatively linked to a coding sequence comprising an INS.

Gritz et al teach the cloning and characterization of the plasmid-borne gene (hph) encoding hygromycin B phosphotransferase from E. coli (e.g. Abstract). Gritz et al teach that when placed in the appropriate shuttle vector, hph allows for direct selection of cells comprising the shuttle vector in yeast as well as for E. coli (e.g. Abstract). This selection varies for different concentrations of hygromycin B and different constructs comprising different transcription initiation points (e.g. Figure 5 & Table II). Thus, Gritz et al teach that different levels of hygromycin B phosphotransferase in a cell expressing the hph gene can be detected by genetic selection. In addition to detecting the levels of hygromycin B phosphotransferase by direct genetic selection, Gritz et al teach a method for directly assaying enzyme activity in a cell extract (e.g. page 181, column 1, last paragraph; Table 1).

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the hygromycin resistance gene in the methods of Pavlakis et al as an indicator to identify instability sequences (INS) of a gene encoding a transcript known or suspected to possess such INS sequences because Pavlakis et al teach it is within the skill of the art to use a gene encoding an mRNA which is expressed at relatively high levels (defined as being stable enough or highly expressed enough such that any decrease in the level of the mRNA or expressed protein can be detected by standard methods) as a reporter gene to identify such instability sequences and because Gritz et al teach that the gene encoding hygromycin B phosphotransferase is sufficiently well expressed that one can assay for its presence by direct genetic selection or by enzymatic assay in either prokaryotic or eukaryotic systems. One would have been motivated to do so in

order to receive the expected benefit of being able to easily assay for protein encoded by the hybrid transcripts comprising the putative INS sequence, as taught by Pavlakis et al, by either enzymatic means or by direct genetic selection, as taught by Gritz et al. Absent any evidence to the contrary, there would have been a reasonable expectation of success in practicing the methods taught by Pavlakis et al with the hph gene, as taught by Gritz et al, to identify putative destabilizing INS regions in a desired gene transcript. In cases in which such a destabilizing element is identified using the hygromycin resistance gene as a reporter, one would necessarily have generated a short-lived transcript drug resistance gene.

The limitation of "a drug resistance gene, as a selection marker", while not indefinite, is extremely broad, encompassing any arrangement or conditions wherein the drug resistance gene can be used in a given cell type to select for cells comprising the vector. Structurally, the limitation implies that the resistance factor expressed by the resistance gene is functional, and that the coding sequence for the drug resistance factor is operatively linked to a promoter active in at least one cell type. There is no further limitation regarding under what conditions the drug resistance gene is usable as a selectable marker (e.g. cell type, drug levels, etc.). Vectors made according to the teachings of the references cited above would include embodiments wherein the INS sequence attached to the hyg^r gene would not result in inactivation of the hygromycin resistance factor (e.g. attachment of the c-fos 3' untranslated INS element to the hyg^r gene). Such embodiments would be structurally indistinguishable from the claimed vector.

Claims 34-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pavlakis et al (U.S. Patent No. 5,972,596; see the entire patent) in view of de la Luna et al (Gene 1988, Vol.

62, pages 121-126). **This is a new rejection. The grounds of this rejection are directed to the embodiments embraced by the rejected claims, and previously specifically recited, wherein the mRNA-destabilizing sequence is operatively linked to the drug resistance gene.**

The teachings of the Pavlakis et al patent (the '596 patent) are described above and applied as before, except:

The Pavlakis et al patent does not explicitly teach an embodiment where the puromycin resistance gene is operatively linked to a coding sequence comprising an INS. The '596 patent doesn't explicitly teach the fusion of a coding sequence for puromycin resistance to any part of the c-fos gene.

The de la Luna et al reference teaches the construction and characterization of different vectors expressing the puromycin-resistance protein (puromycin-N-acetyl-transferase or PAC) for the efficient transformation of mammalian cells (e.g. Abstract). The de la Luna et al reference teaches that one can detect varying levels of PAC expressed from different constructs in COS-1 cells based upon an enzymatic assay (e.g. Table 1). The reference further teaches that one can detect different levels of PAC expression from the different expression constructs by genetic selection for stably transformed cells (e.g. Table II, expressed as the number of stable transformants per 10^6 recipient cells).

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the puromycin resistance gene in the methods of Pavlakis et al as an indicator to identify instability sequences (INS) of a gene encoding a transcript known or suspected to possess such INS sequences because Pavlakis et al teach it is within the skill of the art to use a gene encoding an mRNA which is expressed at relatively high levels (defined as being stable enough or highly

expressed enough such that any decrease in the level of the mRNA or expressed protein can be detected by standard methods) as a reporter gene to identify such instability sequences and because de la Luna et al teach that the gene encoding puromycin resistance is sufficiently well expressed that one can assay for its presence by genetic selection or by enzymatic assay. One would have been motivated to do so in order to receive the expected benefit of being able to easily assay for protein encoded by the hybrid transcripts comprising the putative INS sequence, as taught by Pavlakis et al, by either enzymatic means or by genetic selection, as taught by de la Luna et al. Absent any evidence to the contrary, there would have been a reasonable expectation of success in practicing the methods taught by Pavlakis et al with the puromycin resistance gene, as taught by de la Luna et al, to identify putative destabilizing INS regions in a desired gene transcript. In cases in which such a destabilizing element is identified using the puromycin resistance gene as a reporter, one would necessarily have generated a short-lived transcript drug resistance gene.

The limitation of "a drug resistance gene, as a selection marker", while not indefinite, is extremely broad, encompassing any arrangement wherein the drug resistance gene can be used in a given cell type to select for cells comprising the vector. Structurally, the limitation implies that the resistance factor expressed by the resistance gene is functional, and that the coding sequence for the drug resistance factor is operatively linked to a promoter active in at least one cell type. There is no further limitation regarding under what conditions the drug resistance gene is usable as a selectable marker. Vectors made according to the teachings of the references cited above would include embodiments wherein the INS sequence attached to the pur^r gene would not result in inactivation of the puromycin resistance factor (e.g. attachment of the c-fos 3' untranslated

INS element to the pur^r gene). Such embodiments would be structurally indistinguishable from the claimed vector.

Response to Arguments/103(a) Rejection in Paper No. 11

Applicant's arguments filed in Paper No. 12 in response to rejection of claims 8-9 as obvious over Pavlakis et al in view of DePonti-Zilli et al have been fully considered but they are not persuasive. The response in Paper No. 12 essentially argues: 1) the cited patent (i.e. Pavlakis et al; US 5,972,596) fails to teach a resistance gene operatively linked to a coding sequence containing an inhibitory/instability sequence, or vector comprising the hybrid gene, 2) the patent fails to teach or suggest an expression vector, cells containing an expression vector or a process of producing the same as presently claimed, and 3) the examiner used impermissible hindsight in to combine the recited references.

While, as indicated in the previous action, Pavlakis et al does not *exemplify* an embodiment wherein an inhibitor/instability sequence (INS) is operatively linked to a drug resistance gene, the patent clearly indicates that such drug resistance gene/INS hybrids are within the scope of the invention when it teaches that the neomycin resistance gene and chloramphenicol acetyltransferase genes can be used in the invention as reporters to identify INS sequences (e.g. column 13, lines 12-25). The amended claims now read on any expression vector comprising a selectable marker and an INS sequence, no matter whether the drug resistance gene is operatively linked to the INS sequence, because there is no explicit linkage of the mRNA-destabilizing sequence to the drug resistance gene. In fact, the claims now read on

any prokaryotic drug resistance gene that happens to be on the same vector. As indicated above, such markers on a plasmid expression vector are prima facie obvious.

With regard to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). The rejection made in Paper No. 11 and those made herein do not rely on knowledge gleaned only from applicants' application in order to provide motivation or expectation of success for combining the recited references. Pavlakis et al clearly teach that any reporter gene whose presence can be measured at the RNA or protein level can be used as a reporter in their methods to identify INS sequences in a desired coding sequence (e.g. c-fos). The patent specifically recites two drug resistance genes, encoding neomycin resistance and chloramphenicol acetyltransferase, as examples of indicator genes. Therefore, the motivation to combine the teachings of Pavlakis et al with any other reference teaching a gene for which assays to determine its level of activity are known is provided by Pavlakis et al.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 34-36, 38-39 are rejected under 35 U.S.C. 102(b) as being anticipated by Treisman (Cell, 1985, Vol. 42, pages 889-902; see the entire reference). **This is a new rejection, necessitated by applicants' amendment of the claims in Paper No. 12.**

Treisman teaches the characterization of c-fos RNA stability following serum stimulation and concludes that such stimulation requires a conserved 5' and 3' element (e.g. Abstract). All of the plasmids constructed by Treisman were constructed on a pUC12 backbone such that the c-fos sequences are transcribed in the same direction as the ampicillin resistance gene. The clone comprising the entire c-fos gene was constructed with a 5.4 kb human genomic fragment that necessarily comprises the now well known 3' mRNA-destabilizing sequence (e.g. page 899-900, Plasmid Construction and Preparation). In particular, Treisman describes experiments wherein the in vivo half-life of the full-length human c-fos transcript and various c-fos/B-globin hybrid transcripts are compared. At least one of the hybrids, F/B-FOS3', comprising the 5' and 3' c-fos untranslated sequences attached to the coding sequence for B-globin, is described as behaving similarly to the intact c-fos gene, with rapid efficient induction followed by rapid RNA turnover (e.g. Figure 8B, lanes 5-8; page 898, 1st paragraph). Thus, plasmids pF4 and pF711-FOS3' meet the limitations of having 1) and mRNA destabilizing sequence, and 2) comprising a drug resistance gene as a selectable marker.

Examiner's Comments

It is noted that claims directed towards methods of preparing pre-packaging cells comprising transforming host cells with the vectors described in the instant specification, the

vectors comprising the short-lived transcript drug resistance genes of the invention, would be free of the art and would probably be allowable so long as the claims were narrowly drawn to the types of vectors described in the instant specification for producing retroviral packaging cells. Such claims would probably require a Terminal Disclaimer over copending claims in the parent application (i.e. 09/214,465).

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald G Leffers Jr. whose telephone number is (703) 308-6232. The examiner can normally be reached on 9:30am-6:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (703) 305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-7939 for regular communications and (703) 305-7939 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Gerald G Leffers Jr.
Examiner
Art Unit 1636

AAA
Ggl
February 5, 2003

DAVID GUZO
PRIMARY EXAMINER